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<b>(54) Title:</b> ENCAPSULATION OF ENVIRONMENTALLY SENSITIVE MATERIALS  <b>(57) Abstract</b>  Environmentally sensitive materials such as hygroscopic or deliquescent compounds may be encapsulated in naturally oc- curring or synthetic waxes by the method of this invention. The invention uses wax which, while in the liquid phase, has been sub- jected to a force and thereby transformed into a state which has altered properties. Triglyceride waxes represent one example of waxes which may be used with this invention. Triglycerides formed from long chain saturated unbranched aliphatic carboxylic acids, which normally exhibit polymorphic states upon crystallization, may be transformed in the liquid phase to convert the trig- lyceride to a state which solidifies only in the stable higher melting $\beta$ polymorphic form. Direct mechanical mixing of environ- mentally sensitive core materials with transformed liquid waxes yields capsules of the core material in transformed wax shells. The capsules made by the method of this invention completely enclose the core material and are stable over time. Further, the capsules are free-flowing and may be compounded into tablets. The method of this invention permits encapsulation of core parti- cles over a wide range of sizes.		

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## ENCAPSULATION OF ENVIRONMENTALLY SENSITIVE MATERIALS

Technical Field and Background Art

Encapsulation is the term applied to the formation from  
5 a suitable material of a shell which encloses a core  
material. The capsule thus formed may have as core  
material solids, liquids, gas, or multiphase compounds.  
During the past decade, encapsulation of a broad range of  
10 useful materials has been achieved using a variety of  
encapsulation techniques such as coacervation, thermal  
coacervation, complex coacervation, interfacial polymer-  
ization, and others.

One general purpose of encapsulation is to preserve or  
isolate the core material from its environment until an  
15 appropriate time or condition is present. In these  
situations, the core material is protected from the  
environment by the shell. Such protection is not always  
easily achieved. For instance, one class of materials  
which has been particularly difficult to encapsulate is the  
20 hygroscopic and/or deliquescent compounds. Hygroscopic  
materials readily absorb moisture from their surrounding  
environment and may deliquesce, that is, become liquid by  
absorbing the moisture. The environmental conditions to  
which the more readily absorbing of these materials may be  
25 exposed before they begin to degrade or change phase are  
relatively limited. Often, in order to encapsulate these  
materials, it is necessary to maintain the materials in a  
solvent other than water. Not only may the solvent react  
with the shell material in unpredictable ways, but also  
30 ridding the final capsule of the solvent is often a very  
laborious if not impossible task. When the capsules are  
intended to contain hygroscopic medicants of one form or  
another, it is particularly important that the encapsula-  
tion process not add any potentially deleterious chemicals  
35 to the capsule.

Encapsulation can also be used to protect compounds from  
environmental conditions such as temperature, pH, or  
chemically reactive surroundings. In some cases the shell  
protects the core from oxidizing and reducing environments

which may consist of chemicals to which the core material or the completed capsule may be added.

It is desirable to encapsulate certain other chemical compounds not only for protection of the core compound  
5 itself but to protect or shield the external environment from reaction with the chemical compound forming the core. One common example of this use of encapsulation is the ability to mask the taste and/or odor of a chemical by encapsulation. In this case, encapsulation offers  
10 protection against detection of a bitter or otherwise undesirable taste or odor. Encapsulation of skin and respiratory irritants or toxins is one important way to protect the handlers from exposure.

The advances provided by the method of the present  
15 invention will be discussed with reference to encapsulation of hygroscopic compounds, but it should be understood that the technique is equally applicable both to the protection of other types of core materials from environmental influences as well as to the protection of  
20 the environment from certain core materials.

With respect to hygroscopic materials, not only has it proved difficult to encapsulate hygroscopic and/or deliquescent materials, but it has also proved difficult to find an encapsulating shell material which on the one hand  
25 permits encapsulation with relative ease and speed, and on the other hand is relatively impermeable to water so that the hygroscopic materials, once encapsulated, do not rapidly degrade, change phase, or leak out of the capsule. An additional restraint is imposed if the encapsulated core  
30 material is incorporated in an orally administered medicant. In this case, the shell material must also dissolve/degrade in the stomach or intestinal tract and must not be toxic to the organism.

Given the above constraints of an easily manipulated,  
35 water resistant, digestible shell material, a desirable choice for a shell material would be a naturally occurring or synthetic wax (organic ester) such as one of the

naturally-occurring lipid or fatty acid compounds or a derivative thereof. It is well known that many triglycerides (esters formed from glyceryl and fatty acids in which all three hydroxy groups of the glyceryl molecule are esterified) are relatively insoluble in water and that biochemical pathways exist for their degradation. Unbranched aliphatic carboxylic acids with an even number of carbon atoms and having a chain length between four and twenty-two carbon atoms are most commonly found in naturally occurring triglycerides. These carboxylic acids may be saturated or unsaturated. When all three hydroxy groups of a glyceryl molecule have been esterified with the same fatty acid, it is referred to as a monoacid triglyceride. The longer chain saturated carboxylic acids form triglycerides with higher melting points.

Extensive use has been made of triglycerides in the food preparation industry. For instance, the monoacid triglyceride, glyceryl tristerate, has been widely used as a crystal growth accelerator or initiator in the manufacture of chocolate products and in the compounding of pharmaceutical compositions especially as an aid to tablet formation. As a naturally occurring triglyceride, in moderate concentrations it is not considered toxic in food or chemical preparations meant for human consumption.

In fact, attempts to use the triglycerides in the formation of capsules, including capsules containing hygroscopic compounds, have been tried but have achieved only limited success. Usually, the triglycerides are present as granulating agents. Examples from the prior art are the patents of Ando et al., Canadian patent 1,225,861, and Nishimura, EPO application No. EPO 276,781 A2. However, nowhere in the previous art has anyone succeeded in forming an entire stable shell wall of a capsule out of a triglyceride.

The major obstacle to the use of triglycerides as shell material is the fact that triglycerides are polymorphic; that is, a given triglyceride may solidify in substantially

different crystalline forms even within the same mass. Complicating their use even further is the fact that triglycerides exhibit a special form of polymorphism, designated monotropic polymorphism, in which the lower melting point crystal forms are unstable and convert over time to a more stable form with the conversion rate dependent upon the temperature of the material. Monotropic polymorphic conversion always takes place in the direction towards the more stable crystal forms. Such conversion between polymorphic forms involves a structural rearrangement of the molecules and such rearrangement is inconsistent with the encapsulation requirement that the shell material possess a stable structure.

For example, when melted, cooled and solidified rapidly, the triglyceride, glyceryl tristerate, first hardens in a glass-like amorphous form which then converts over time to a crystalline form (the alpha " $\alpha$ " form) having a hexagonal crystal lattice structure and a melting point of about 54° C. This polymorphic  $\alpha$  form is only relatively stable. If heat is provided to the  $\alpha$  form material, the glyceryl tristerate will convert over time through an unstable intermediate form (the beta-prime " $\beta'$ " form) to a yet higher melting point form (the beta " $\beta$ " form) having a triclinic crystal lattice structure with a melting point of about 72° C. Once the conversion to the higher melting point  $\beta$  form is complete, the  $\beta$  form is stable.

Such polymorphism presents problems in the use of the triglycerides and especially any attempt to create stable capsule shell structures from them. While many of the triglycerides, such as glyceryl tristerate, are available as powders in relatively pure  $\beta$  form, these  $\beta$  forms are obtained from crystallization of the material from solvents. The powders themselves are usually not usable in most encapsulation processes without the use of solvents, since once the triglyceride is melted and allowed to recrystallize, typically both the lower  $\alpha$  and higher  $\beta$  melting point polymorphs are present in the resulting

material. One would thus expect that a capsule shell made from such a polymorphic material would not form a complete and stable envelope around the core material of the capsule. Thus, from the teachings of the prior art, it appears that the natural triglycerides are not likely candidates for use alone as encapsulating shell materials.

#### Disclosure of the Invention

The method of the present invention allows the encapsulation of environmentally sensitive materials including hygroscopic and/or deliquescent compounds in a waxy shell without the use of non-aqueous solvents. The shell material consists of a member of the class of naturally occurring or synthetic waxes which has been transformed while in the liquid phase to a form from which shells possessing superior characteristics may be generated. For those waxes which are polymorphic, the transformation yields a liquid phase of the wax which only crystallizes/hardens in the higher melting point form. The results obtained with the triglyceride waxes clearly demonstrate the success obtained with the method of this invention. In order to obtain the liquid phase of the triglyceride which solidifies in only the higher melting point  $\beta$  polymorph, liquid native triglyceride is transformed by being subjected to a force. For instance, the liquid triglyceride may be placed within an enclosed chamber attached to a piston and subjected to a stroke cycle of the piston. An example of another method of subjecting the triglyceride to force is to expose the molten triglyceride to ultrasound delivered by an ultrasonic transducer immersed in the liquid wax. Liquid triglycerides transformed in either manner exhibit only the stable higher melting point  $\beta$  structure upon cooling and solidification.

The invention utilizes the force transformed waxes as one component of a two-component mixture in which the transformed wax is mechanically mixed while still in a liquid phase with the second component, the core material

to be encapsulated. Complete mixing of the transformed liquid wax shell material with the core material, followed by cooling of the mixture, produces encapsulated core material. The capsules thus formed exhibit

5 characteristics unobtainable with the prior art. For instance, if a hygroscopic and/or deliquescent core material is encapsulated, and the capsules are exposed to a humid environment, the capsules remain free-flowing and may be readily formed into tablets by procedures well known  
10 in the art. In addition the transformed waxy shell material retains the hygroscopic and/or deliquescent core material within the capsule without loss of chemical concentration or activity.

It is an object of this invention to produce capsules  
15 having shell walls formed from naturally occurring or synthetic waxes, which have been transformed by being subjected to force, to possess improved shell characteristics.

Another object of this invention is to produce capsules  
20 containing environmentally sensitive core materials which are isolated from the environment by waxy shell walls.

It is another object of this invention to provide a method whereby environmentally sensitive core materials, including hygroscopic and/or deliquescent materials, may be  
25 encapsulated.

Another object of this invention is to use naturally occurring and synthetic waxes which, while in a liquid phase, have been transformed by being subjected to force as shell materials for encapsulation.

30 It is another object of this invention to use triglycerides as a shell material for encapsulation.

It is a further object of this invention to encapsulate compounds in a shell material without the use of carrier solvents.

35 A further object of this invention is to encapsulate compounds in a shell material without the use of non-aqueous solvents.



Yet another object of this invention is to prepare a capsule having a choline chloride core.

A further object of this invention is to make a capsule with a shell which is non-toxic and digestible.

5 Another object of this invention is to protect by encapsulation core materials from exposure to the external environment surrounding the capsule.

A further object of this invention is to improve the handling characteristics of certain materials through  
10 encapsulation.

Yet another object of this invention is to provide a protective shell for an environmentally sensitive medicant or vitamin so that the capsules may be incorporated into a tablet designed for oral administration.

15 Other useful objects of the invention will become apparent to those skilled in the art from the disclosure which follows.

#### Description of the Drawings

Figure 1 is a differential scanning calorimeter (DSC) spectrum showing the endothermic melting point/peak of the  
20  $\beta$  polymorph of crystallized glyceryl tristerate (Dynasan 118) as provided by the manufacturer.

Figure 2 is a DSC spectrum of glyceryl tristerate which has been melted and resolidified showing the endothermic  
25 peaks corresponding to the  $\alpha$  and  $\beta$  forms and the exothermic heat of crystallization.

Figure 3 is a DSC spectrum of glyceryl tristerate which has been melted, treated with one piston stroke cycle, and resolidified.

30 Figure 4 is a DSC spectrum of glyceryl tristerate which has been melted, treated with 5 successive piston stroke cycles, and resolidified.

Figure 5 is a DSC spectrum of glyceryl tristerate which has been melted, treated with ultrasound, and resolidified.

35 Figure 6 is a partial schematic outline of the method of the invention.

Figure 7 is a schematic diagram of the piston apparatus

used to treat waxes.

Figure 8 is schematic diagram of the ultrasonic apparatus used to treat waxes.

Figure 9 is a schematic diagram of the mixing apparatus  
5 used to encapsulate by the method of this invention.

Detailed Description of the Invention

The method of this invention relies in part upon the discovery that subjecting liquid waxes to a force transforms those waxes into a different liquid state  
10 characterized by the fact that when the waxes solidify, they do so in forms different from those forms into which they would solidify except for the application of the force. The transformed waxes exhibit altered characteristics which make them superior capsule shell  
15 material. For instance, transformation converts waxes such as the triglycerides (which normally crystallize in multiple polymorphic forms) into liquid forms which solidify in only a single polymorphic state, that of the stable higher melting point  $\beta$  structure. That discovery is  
20 disclosed in a co-pending U.S. patent application entitled, "Method and Apparatus for Inducing Transformations in Waxes" filed on even date herewith.

The term "wax" as used in this application is intended to have as broad a meaning as possible and contemplates  
25 organic ester or waxy compounds derived from animals, vegetables, and minerals including modifications of such compounds from all three sources in addition to those materials having similar properties which are synthesized by man. Examples of some of the naturally occurring and  
30 synthetic waxes which may be used after transformation, either alone or in combination, with the method of this invention to form capsule shells about core materials are shown below in Table 1.

TABLE 1

	Glyceryl TRISTEARATE	Glyceryl DISTEARATE
	DYNASAN <sup>TM</sup> 110, 114, 116, 118	STEROTEX <sup>TM</sup> HM, K
	CANOLA WAX/OIL	COTTON FLAKES
5	SOYA FLAKES	CASTOR WAX
	RAPESEED WAX	BEESWAX
	CARNAUBA WAX	CANDELILLA WAX
	MICROWAX (PETROLEUM BASED)	BOLER <sup>TM</sup> WAX 1014
	SPECIAL FAT <sup>TM</sup> 42, 44, 168 T	BE SQUARE <sup>TM</sup> WAX #195A
10	BE SQUARE <sup>TM</sup> WAX #195W	ENERGYBOOSTER <sup>TM</sup>
	ASTOR <sup>TM</sup> WAX 180	ASTOR <sup>TM</sup> WAX 150

Clearly, for encapsulation purposes, a transformed wax should be used which exists as a solid at the temperature at which the capsules will be stored and used. Normally, therefore, waxes which are solid at room temperatures will be used. For some applications in cold environments, a lower melting point wax could be used. Similarly, if the capsule will be subjected to higher temperatures, a higher melting point wax should be chosen. The method of this invention is clearly demonstrated by its application to the triglyceride waxes.

The triglycerides most useful with the present invention are unbranched aliphatic carboxylic acid esters of glyceryl. In addition, in order to form a stable shell which is not subject to rancidity, triglycerides formed from saturated carboxylic acids should be used. Generally, the higher the melting temperature (the longer the carbon chain length) of the triglyceride, the better capsule material the triglyceride makes after treatment.

Triglycerides may be obtained commercially in a variety of purity grades. Commercial preparations of triglycerides start with natural products in which a number of different triglycerides are associated with each other. Processing not only saturates the acid substituents but reduces the variety of triglycerides in the final material. It has been found that the purer the starting triglyceride materi-

al, the better it serves after transformation as a shell material. The most suitable triglyceride for use after transformation as a shell material of which Applicant is aware is the monoacid triglyceride, glyceryl tristerate ("tristearin") formed by the esterification of 18-carbon stearic acids with all three hydroxy groups of glyceryl.

The most suitable commercial grade of tristearin for forming shells after transformation of which the Applicant is aware is the product having the trade name "Dynasan 118" which is manufactured by Dynamit Nobel, a subsidiary of Huls America. Dynasan 118 is a highly purified material from a vegetable source. As it is supplied by the manufacturer, Dynasan 118 is a white microcrystalline powder crystallized in the  $\beta$  form as can be seen by the differential scanning calorimeter (DSC) spectrum of a sample of Dynasan 118 shown in Figure 1. The presence of only a single endothermic peak centered at approximately 72° C. indicates that only a single polymorphic form is present with a melting point within the melting temperature range of the  $\beta$  form.

Like other triglycerides, when the Dynasan 118 tristearin is heated to a molten phase and allowed to cool, it crystallizes in both the  $\alpha$  and  $\beta$  forms as can be seen in Figure 2 where the Dynasan 118 was first heated to 125° C and then resolidified. The polymorphic  $\alpha$  form melts at a lower temperature and is seen in the DSC spectrum of Figure 2 as an endothermic peak centered at approximately 54° C. The stable polymorphic  $\beta$  form melts at a higher temperature and is seen in the DSC spectrum of Figure 2 as the more prominent endothermic peak centered at approximately 72° C. The resolidified tristearin obviously has coexisting within it both crystal structures. The upward (exothermic) peak centered at approximately 57.5° C between the endothermic peaks for the  $\alpha$  and  $\beta$  forms in the DSC spectrum of Figure 2 is the exothermic heat of crystallization. This Figure shows the classic DSC spectrum of the heat of crystallization of tristearin.

A few comments are in order with respect to the DSC spectra presented in the figures. First, the absolute height (or depth) of the peaks in the DSC spectra are reflective only of the mass of the sample used to generate that curve. Thus, differences in the height (or depth) of a peak from one spectrum to another are not significant in terms of identifying the polymorphic forms in which the material exists. The different polymorphic forms are distinguished by the fact that they melt at different temperatures.

The relative proportions of the polymorphic  $\alpha$  and  $\beta$  forms which crystallize from melted tristearin will vary depending upon the heating and cooling regimen to which the tristearin sample has been subjected. However, Figure 2 is representative of tristearin when it is melted and resolidified. It is obvious from the width of the peaks in the DSC spectra of Figures 1 and 2 that a range of melting points exist for both the  $\alpha$  and  $\beta$  forms. The exact reason for this is unclear.

Applicant is aware of two possible explanations for the width of the peaks. First, it is suggested that even in the solid (crystallized) state, some non-ordered or randomly ordered tristearin may be trapped within the crystalline structures, thereby locally altering the crystal structure and its melting point. The second explanation is that, because of the nature of the commercial preparation of the tristearin, a totally pure, homogeneous material has not been obtained. For instance, not all of the stearic acid moieties may have been totally saturated. It is also possible that some shorter or longer chain carboxylic acids may have participated in the esterification, whether saturated or not. The range of compounds therefore yields a range of melting points which is reflected not only in the width of the DSC peaks but also in the fact that different samples have slightly different/shifted principal melting points. Applicant believes this second explanation is most likely.

Applicant has observed that tristearins from different manufacturers and/or derived from different starting materials exhibit varying peak widths as well as slightly shifted melting points of the polymorphic forms as measured by the DSC. However, there may also be other factors at work which are unknown to the Applicant.

Figures 3 and 4 show the DSC spectra of solidified tristearin which, while in a liquid molten phase, was subjected to the force of compression/expansion cycles of a piston stroke before solidification. The  $\alpha$  and  $\beta$  peaks are identified by appropriate legends in both Figure 3 and Figure 4. In Figure 3 the tristearin, while in the molten phase at 145° C, was subjected to the force of one stroke cycle of the piston. The small endothermic peak centered at approximately 60° C suggests that some residual  $\alpha$  form is still present. However, the relative magnitude of the larger  $\beta$  peak centered at approximately 76° C demonstrates that the tristearin has solidified predominantly in the  $\beta$  form. The piston applied a pressure of about 4400 pounds/inch<sup>2</sup> during its stroke cycle. As can be seen by comparing Figure 3 with Figure 2, subjecting tristearin to the force of the piston stroke modified the molten phase of the tristearin wax so that the wax solidified in a different manner than it would have without the application of the force.

Figure 4 shows the DSC spectrum of solidified tristearin which, while in the molten phase at 145° C, was subjected to five stroke cycles of the piston. The presence of a single peak centered at approximately 77° C clearly shows that the solidified tristearin exists in only the  $\beta$  form. There is no indication of any residual polymorphic  $\alpha$  form present. The piston applied a pressure of about 5500 pounds/inch<sup>2</sup> during each stroke cycle. The tristearin in both Figures 3 and 4 was first heated to 145° C, piston treated, and then cooled to solidification. Complete transformation of the molten wax to a molten form which solidified in only the  $\beta$  polymorphic form required five

piston stroke cycles at 5500 pounds/inch<sup>2</sup> for the wax sample of Figure 4. As discussed more fully in the corresponding application referred to earlier, transformation of the wax seems to depend on both the temperature of the liquid tristearin when subjected to force as well as the total force applied.

The polymorphic form of the untreated (native) tristearin wax represented by the solidified sample of Figure 2, when used in an encapsulation process, does not form a suitable shell for the protection of core materials, especially environmentally sensitive materials. When used to coat or encapsulate a core material, the polymorphic form allows greater access to the core material by external conditions such as moisture, oxidizing or reducing materials, and other chemical reactants. It has been discovered that, when used to coat or encapsulate a core material, glyceryl tristearate which has been transformed by being subjected to a force so as to be converted to a material which solidifies in substantially the all  $\beta$  polymorphic form provides a more complete barrier against penetration to the core material by external conditions. Although core materials may be encapsulated with either the polymorphic or transformed (all  $\beta$  form) of glyceryl tristearate, it is the transformed, all  $\beta$  form, which yields the superior shell and offers the best protection for the core material.

Figure 5 is a DSC spectrum of resolidified ultrasonically transformed tristearin. The tristearin was melted, heated to 90° C, and subjected for a period of ten minutes, while being stirred, to the force of ultrasound at an intensity level of 25 watts/cm<sup>2</sup>. As can be seen from Figure 5, upon solidification, the ultrasonically transformed tristearin wax hardened in the all  $\beta$  polymorphic form yielding the customary  $\beta$  form peak centered at approximately 71° C, similar to the  $\beta$  form peak seen in Figures 1 and 2. However, it should be noted that the time needed to transform the tristearin wax to the all  $\beta$  form by

means of piston stroke cycles required only a few seconds while the ultrasonic transformation required ten minutes. However, it is possible that either a greater total force applied by a higher power ultrasonic transducer or a  
5 different transducer geometry, cavity shape, or exposure area such as in a flow cell may produce the transformation in less time than the device presently available to Applicant.

Figure 6 schematically outlines the method of the  
10 present invention. In step 1, the selected wax is, if necessary, first heated to above its melting point with constant stirring to assure uniformity of temperature. The liquid wax is subjected to force such as by a piston stroke cycle in step 2 or as by ultrasonic exposure in step 2'.  
15 After the wax is transformed, it is mixed in step 3, while still in the liquid phase, with the core material in a mechanical mixer for a period of time sufficient to ensure complete coating of the core material by the liquid transformed wax. During the mixing, the mixing vessel may  
20 also be kept heated. The core compound to be encapsulated may be preheated as in step 5 prior to mixing with the transformed wax. Preheating the core material is not absolutely necessary, but has been found to produce superior capsules.

25 The pre-heating of the core material and the heating of the mixing vessel during the mixing of the transformed liquid wax with the core material prevents too rapid solidification of the wax on the core material. Even if the core material is not preheated and the mixing container  
30 is not heated, encapsulation by the transformed wax will occur. However, in such instance, more wax may be needed than is required when both the core material and the mixing vessel are kept warm during the mixing/coating/encapsulation procedure. After the transformed liquid wax and the  
35 core material have been thoroughly mixed and the capsules formed, the capsules are permitted in step 4 to cool so that the transformed wax solidifies.



By this method, capsules may be formed using a wide range of proportions of capsule shell material, transformed wax, to core material. For instance, for transformed tristearin it has been found that a 75%/25% ratio by weight of core material to transformed tristearin shell material yields good capsules. However, a larger percentage of capsule shell material may be used if thicker capsule walls are desired. It has been found that using the mixer described, shell weight percentages less than 20% do not adequately coat core material particles. It is possible that a different mixer might allow the coating of particles with less than 20% shell. Capsules with 90% shell have easily been formed. Further, the particle size of the core material being encapsulated is not restricted by the method of this invention. Thus, microcapsules may be formed, when the core material is first reduced in size by means well known in the art to micron size, while much larger capsules (on the order of hundreds of microns) may be formed on larger core particles by this process.

Environmentally sensitive core materials may be simply and quickly encapsulated in this manner. The transformed wax shell isolates the sensitive core material from the surrounding environment, or, depending on the core material, it may be that the transformed wax shell isolates the surrounding environment from the core material. Some of the environmentally sensitive materials which may be encapsulated with the method of this invention are shown in Table 2.

TABLE 2

30	CHOLINE CHLORIDE	CHOLINE BITARTRATE
	CHOLINE SULFATE	CALCIUM CHLORIDE
	VITAMINS A, B, C, D, E	FOLIC ACID
	ASCORBIC ACID	PYRIDOXINE HCl
	THIAMINE MONONITRATE	NIACINAMIDE
35	OXIDATION SENSITIVE COMPOUNDS	HYGROSCOPIC COMPOUNDS
	REDUCTION SENSITIVE COMPOUNDS	

Choline chloride is one example of an environmentally sensitive material which has been successfully encapsulated by the method of this invention. Choline is a growth stimulant and a metabolic precursor required by the central nervous system for proper functioning. Choline chloride is extremely hygroscopic. Because the choline chloride salt is so hygroscopic and difficult to work with, less hygroscopic and more stable choline bitartrate is commonly used where choline is to be compounded or encapsulated. However, since choline represents a smaller fraction of the molecular weight of choline bitartrate than it does of choline chloride, the use of choline bitartrate as a core material results in capsules having a lower choline content for a given core weight and size.

Experiments by the Applicant have shown that it is possible to use the wax, glyceryl tristerate, to encapsulate choline chloride by another method than the method of this invention. For instance, if powdered  $\beta$  form tristearin is dissolved in warm to hot dichloromethane (methylene chloride) and choline chloride is added to the dissolved tristearin, choline chloride capsules having a high percentage  $\beta$  form tristearin shell will be formed as the dichloromethane is evaporated away. However, DSC spectra of such capsules show high temperature endothermic peaks not associated with either any polymorphic form of tristearin or with choline chloride. Apparently, some unknown chemistry has taken place.

Thus, because of the possibility of solvents such as dichloromethane reacting with either the wax (tristearin) or the core material (choline chloride) as well as the likelihood of contamination of the capsule with residual dichloromethane, formation of capsules by the method of the present invention is preferred over preparation from solvents. In fact, the method of this invention represents a major advance in the art of encapsulating materials since: 1) no additional chemicals are introduced or needed in the encapsulation process; 2) the core and shell

materials are not subjected during encapsulation to unusual or physically stressful conditions; and 3) no post-encapsulation treatment (chemical, thermal, physical, etc.) is required to stabilize the capsules.

5 In the above examples, a force applied to the liquid waxes transformed the waxes to a different state. An example of an apparatus for producing the transforming force is shown schematically in Figure 7. The apparatus, illustrated in Figure 7, consists of a reservoir 1 having a stirrer 11 located so as to stir the wax contents 3 of reservoir 1. Reservoir 1 may be heated, if necessary as in the case of a wax which is solid at room temperature, by heating coils 2, and the temperature of the wax material 3 within reservoir 1 determined by temperature measuring apparatus 18. A transfer conduit 14 leads to piston assembly 13. Piston assembly 13 consists of chamber 15, having inlet valve 6 and outlet valve 7 at opposite ends, to which is connected piston housing 4 which has within it movable piston 5. Movable piston 5 is displaced within housing 4 by motor 16. Motor 16 may be hydraulic, air, or electrically powered. Valves 6 and 7 may be solenoid valves, manually operated valves, or automatic check valves. Output transfer conduit 17 is connected to piston assembly 13 at exit valve 7 and leads to either a mixing or storage container. Transfer conduit 14 leading to piston assembly 13, piston chamber 15, and transfer conduit 17 leading from piston assembly 13 may be heated, if necessary, with heating coil 12 to maintain the temperature of the wax material 3 as it passes to, through, and from piston assembly 13. The mixing or storage containers may be heated, if necessary, to maintain the temperature of the transformed wax material.

To prepare transformed waxes for use in the encapsulation process, native wax which is to become shell material is first placed in reservoir 1 where, if necessary, it is melted and maintained above its melting point. Alternatively, premelted or liquid wax may be

placed in reservoir 1. The liquid wax is stirred by stirrer 11 until it has a uniform temperature as determined by temperature measuring apparatus 18. In the preferred embodiment, reservoir 1 is located above piston assembly 13 so that the liquid wax 3 is gravitationally fed to piston assembly 13. Liquid wax 3 is admitted to chamber 15 where it is transformed as piston 5 is driven by motor 16 through its positive and negative displacement cycle within housing 4. The liquid wax 3 is shown under pressure in chamber 15 as wax 8. After admitting liquid wax 3, valves 6 and 7 may be closed while the piston cycles, subjecting the liquid wax to force by alternately applying and relieving pressure on the wax within closed chamber 15. Alternatively, the valve action may be adjusted to provide a semi-continuous flow of liquid wax through chamber 15. This can be accomplished by using check valves for both inlet valve 6 and outlet valve 7. As the piston is raised, the pressure within chamber 15 drops below the outside ambient pressure. Check valve 7 prevents previously transformed material from reentering chamber 15 while check valve 6 permits a quantity of liquid wax 3 to be drawn into chamber 15. As piston 5 begins the downward half of its stroke cycle, both check valves 6 and 7 close for a period of time allowing pressure to build up within chamber 15. At some point the pressure on the liquid wax 3 exceeds the pressure setting of check valve 7 which then opens, permitting the transformed wax to flow out of chamber 15 into transfer conduit 17.

As shown earlier with reference to Figure 5, complete transformation of molten tristearin at 145° C to a molten state which will solidify substantially in the all B form is achieved after five repetitive strokes of piston 5 at approximately 5500 pounds/in<sup>2</sup> chamber pressure. Typically, only a couple of seconds are required to transform the wax shell material in this manner. Thus, the throughput of transformed wax shell material is very high even for a small compression chamber. In the preferred embodiment of

the piston apparatus, piston assembly 13 consists of an air driven hydraulic pump such as that manufactured by S.C. Hydraulic Engineering Corporation, Model No. SC-10-600-8. In such a pump, the force exerted by the piston on the liquid wax shell material within the compression chamber can be regulated by the choice of air pressure supplied to the motor. For the Model SC-10-600-8 pump a minimum of approximately 35 pounds/inch<sup>2</sup> inlet pressure is required to activate the pump. Typical inlet pressure ranges to the motor which were found to produce sufficient force on the piston vary from 40 to 60 pounds/inch<sup>2</sup> of pressure. These inlet pressures result in design pressures in the compression chamber of approximately 4400 to 6600 pounds/inch<sup>2</sup> since the pump has a hydraulic pressure multiplying effect of approximately 110. Chamber pressures as high as approximately 9360 pounds/inch<sup>2</sup> have been used with other pumps used to successfully transform the waxes.

The transformed wax shell material 19 may either be collected for later use in a storage container heated, if necessary, to keep the material in the liquid phase or may be immediately used for encapsulation.

An example of a second apparatus for producing the transforming force is shown in Figure 8. A treatment container 20 may be heated, if necessary, to melt a wax which is solid at room temperature, by heater/stirrer 21 which is a combination heating element and magnetic stirrer. The native wax 30, which is to be transformed, in either liquid or solid phase is placed in container 20. If necessary to maintain as a liquid, wax 30 may be heated by heater/stirrer 21 while being stirred by magnetic bar stirrer 22 driven by heater/stirrer 21 and brought to a uniform temperature as determined by temperature measuring apparatus 23. After the wax 30 has reached the desired uniform temperature, horn 24 of ultrasonic converter 25 is placed into the liquid wax 30. Converter 25 is connected by cable 26 to ultrasonic generator power supply 27. Ultrasound 28 is applied to liquid wax 30, once again

resulting in transformation of liquid wax 30 into a liquid state which forms a superior shell when used for encapsulation. For tristearin, a temperature of 90° to 145° C is usually used. Typically, the molten tristearin is subjected to the force of the ultrasound for a period of ten minutes at an intensity level of 25 watts/cm<sup>2</sup>. Stirring is continued during the application of ultrasound to ensure exposure of all the molten tristearin to the ultrasound. Once the conversion is complete, the transformed molten tristearin shell material may be stored in a heated container or used immediately to encapsulate the core material.

Figure 9 shows the apparatus used to encapsulate core materials by the method of this invention. Transformed liquid wax shell material 31 is added along with core material 32 to mixing container 33. Mixing container 33 may be heated by a heating mantle or jacket 34. The core material 32 and transformed liquid wax shell material 32 are mixed by mixer/stirrer 35. Mixer/stirrer 35 provides mechanical agitation to the mixture of core material 32 and shell material 31 to ensure complete coating/encapsulation of the core material 32 by the liquid wax shell material.

Mixer/stirrer paddle 36 is powered by motor 37 which in the preferred embodiment provides both a rotating and reciprocating action to stirrer paddle 36. Transformed liquid wax shell material 31 solidifies around core material 32 as the mixture cools. Depending on the melting point of the transformed wax, the mixture may be cooled by: 1) removing heater 34 after mixing is complete; or 2) gradually reducing the heat supplied by heater 34 to container 33 during mixing; or 3) cooling/chilling container 33 during mixing. Once solidified, and as long as the ambient temperature is below the melting point of the transformed wax, the transformed wax shell material creates a permanent coating over the core material particle, forming a capsule.

The particle size of the initial core material 32 will

basically determine the size of the resulting capsule. Depending upon the size of the starting core material, the resultant capsule may be classified as either a microcapsule or a macrocapsule recognizing that these terms are imprecise.

5 For molten transformed waxes such as tristearin, the encapsulation process can be accelerated to some extent by chilling container 33 during agitation of the core and shell mixture. However, best results are obtained by  
10 cooling the core and shell mixture slowly while continuing the mixing agitation. To facilitate encapsulation, the core material may also be preheated to a temperature below that of the molten transformed wax shell material before mixing with the transformed shell material.

15 Since no solvent or carrier liquid is used in the encapsulation process of this invention, not only is there is no possibility of contamination of the final capsule by such solvents or carriers, but any material may be encapsulated without regard to whether the core material  
20 reacts with such solvent or carrier. In addition, any special handling or storage conditions for environmentally sensitive materials (i.e., inert atmosphere, vacuum, etc.) are easily employed with the encapsulation method of this invention. Hygroscopic and deliquescent compounds may be  
25 successfully encapsulated by the method of this invention since such materials may be mixed in the dry state with the transformed liquid shell material to form capsules without exposure of the hygroscopic core materials to residual water in a solvent or carrier. No special pretreatment or  
30 storage of the hygroscopic core material is required beyond normal handling precautions. Since encapsulation occurs very quickly once the core and shell are mixed, and the shell hardens relatively quickly by cooling, hygroscopic core materials need not be exposed to a potentially  
35 destructive wet atmosphere for a prolonged period of time during processing. In fact, one of the general benefits of this method of encapsulation compared to prior art methods

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is the significant reduction of the overall time needed to encapsulate.

Using the method of this invention, it is possible to add additional layers of shell material to the capsules by repeatedly mixing and coating already formed capsules with transformed liquid wax shell material. However, great care must be taken in controlling the temperature of the transformed wax shell material added to the capsules to avoid melting the already existing wax shell structure.

When used as shell material in the encapsulation process of this invention, transformed waxes produce superior shells which are more resistant to environmental conditions, and which, therefore, protect more fully the core materials from environmental influences. Even for extremely hygroscopic materials, such as choline chloride, which heretofore have been virtually impossible to encapsulate, the transformed waxes yield remarkably improved results.

As mentioned, choline chloride is an example of an extremely hygroscopic compound successfully encapsulated by the method of this invention. Using choline chloride as the core material and transformed tristearin as the shell material, capsules of choline chloride are obtained having stable shell walls which do not degrade over time. The choline chloride capsules are also free-flowing; that is, no clumping or agglutination of the capsules occurs, and they remain free to slide by one another. This makes such choline chloride capsules formed by the method of this invention useful for forming into tablets by means well known in the art. Choline chloride capsules formed by the method of this invention appear in micrographs to have a complete and unbroken tristearin shell. As mentioned earlier, various ratios of core material weight to shell weight may be utilized but it has been found that, for choline chloride, a 75%/25% percent ratio by weight of core to shell material produces satisfactorily encapsulated choline chloride.



Capsules of choline chloride which are formed by the method of this invention do exhibit a gain in weight over a period of time upon continuous exposure to humid atmospheric conditions. This gain in weight is attributed to either water adsorption onto the capsules or water absorption by the capsules. To measure the relative weight gain over time, comparison is made to choline bitartrate which has been coated with silicon dioxide particles. Since choline bitartrate is much less hygroscopic than choline chloride, it is frequently used where choline must be compounded. However, the higher molecular weight of the choline bitartrate makes it unsuitable for many applications where choline is needed. Table 3 illustrates the percentage weight gains seen for four samples: untreated choline chloride, choline bitartrate, choline chloride coated with melted and hardened, non-transformed, native tristearin, and choline chloride coated with transformed tristearin.

TABLE 3

COMPARISON OF MOISTURE ABSORPTION OF ENCAPSULATED CHOLINE CHLORIDE VS. UNTREATED ADSORPTION CONTROL SAMPLES

25	SAMPLE MATERIAL	WEIGHT GAIN OVER 3 HOURS 100% HUMIDITY	WEIGHT GAIN OVER 6 HOURS 100% HUMIDITY	QUANTITY OF CHOLINE PRESENT IN SAMPLE
30	CHOLINE CHLORIDE RAW	21.7 %	36.2 %	85 %
35	CHOLINE BITARTRATE SiO <sub>2</sub>	8.0 %	13.2 %	47 %
40	ENCAPSULATED CHOLINE CHLORIDE IN DYNASAN -118; NATIVE 70:30 CORE/SHELL	20.8%	35.0 %	59.5 %
40	ENCAPSULATED CHOLINE CHLORIDE IN DYNASAN -118; TRANSFORMED 70:30 CORE/SHELL	18.3 %	29.5 %	59.5 %

(averages over 5 samples - absolute weight increases by %)

It can be seen from Table 3 that choline chloride capsules made with native or transformed tristearin shells gain more weight than does the choline bitartrate but much less weight than the untreated choline chloride. The weight gained versus the actual amount of choline present in the samples shows a marked improvement for the transformed wax capsules over the native wax capsules and for the transformed wax capsules is almost equivalent to that for raw choline chloride. In these experiments, after six hours much of the raw choline chloride deliquesces, leaving some remaining material resting in a small pool of liquid. Similarly, after six hours the native wax capsules had moisture droplets or beads on their surface. However, after six hours the capsules made with transformed wax shells remained visibly dry and free flowing. Thus, the principal problem with working with choline chloride, that of its hygroscopicity, has been overcome by encapsulation in the transformed wax shell.

Clearly, shells formed from native tristearin are not as effective in preventing weight gain as are shells formed from transformed tristearin. This is believed to be due to the presence of multiple polymorphic states in the untreated material which degrade the structural integrity of the shell.

The choline chloride capsules formed with transformed tristearin shells remain free-flowing even after exposure to a 100% humidity environment with its accompanying weight gain, and microscopy shows no change in the structure of the shell. Furthermore, after extended exposure to humid atmospheric conditions, analysis of the choline content of the transformed tristearin choline chloride capsules indicates that the choline which was originally encapsulated remains within the capsule and active.

As mentioned, the reasons for the weight gain are not entirely clear. It is possible that some water may be absorbed into the shell layer interstitially between the

waxy tristearin molecules. It is also possible that some of the water reaches the choline chloride core of the capsules. Another possibility is that water adheres to the surface of the capsules, and, finally, it is possible that some residual choline which was not encapsulated during the mixing adheres to the surface of the capsules and may be absorbing the water. However, micrographs show no indication of such residual choline chloride crystals on the outside surface of the capsule shells. Whatever the reasons for the weight gain, the method of this invention produces capsules of choline chloride core in a transformed tristearin shell which remain free-flowing and retain the choline within the capsules without leaking.

In yet another embodiment of the invention, the core material, such as choline chloride, may be pre-mixed with the liquid wax before the wax is subjected to force. Subjecting the mixture to force, such as by piston stroke cycles, yields capsules with the same characteristics as the capsules described above. However, this method results in frequent jamming of the piston assembly.

It is also possible to add various additives to the liquid waxes either before or after subjecting the waxes to force. These additives may act to retard expansion of the waxes upon resolidification. Two such materials which have been added are methylcellulose and ethylcellulose. Ethyl or methyl cellulose added to tristearin after transformation, but prior to mixing with choline chloride, results in capsules of choline chloride which gain much less weight when subjected to a 100% humidity environment than capsules formed from transformed tristearin shells. The choline chloride capsules formed from transformed tristearin to which methylcellulose was added after transformation of the wax similarly are free-flowing, capable of being made into tablets, and contain the choline over time with no loss of choline activity. These capsules often form superior tablets when methylcellulose, ethylcellulose, or similar cellulosic compounds are used as

fillers in the tablets.

The ability to encapsulate environmentally sensitive materials, such as those which are hygroscopic and deliquescent, with a transformed wax shell by simple mechanical mixing of the core and shell materials opens the door to the successful encapsulation of previously difficult core materials. No special treatment of the core material is necessary for the encapsulation process of this invention, nor is the use of non-aqueous solvents required. One direct result is the production of capsules containing no chemical contaminants introduced by the encapsulation process. The resulting capsules are not only stable mechanically and chemically, but are free-flowing and therefore suitable for making into tablets or other compounding.

Further, the capsule size range which can be achieved by the method of this invention is not limited either by the core material or the wax shell material. Generally, the transformed liquid wax will encapsulate any core with which it is mechanically mixed. The capsules assume the size of the underlying core particles. This results in much simpler manufacturing requirements. Additionally, the time required for encapsulation by this method is relatively short. The wax may be transformed immediately prior to encapsulation of the core material or may be transformed and held in the liquid phase for an extended period of time before it is used to encapsulate.

At this time, Applicant is unaware of why subjecting the waxes to force is successful in transforming the waxes to a state which yields superior shells, and, in the case of polymorphic waxes such as tristearin, into a state which solidifies only in the  $\beta$  polymorph. However, both apparatuses described above successfully achieve this transformation, and waxes, including tristearin, transformed by either apparatus yield good capsules of choline chloride.

Several possible physical mechanisms may account for the

transformation of the waxes by the applied force. For those polymorphic waxes, such as tristearin, which convert to a molten state which hardens in the stable higher melting point  $\beta$  polymorph, a possible mechanism may be that at the high pressure achieved as the piston is forced against/into the molten wax within chamber 15, the molten wax begins to crystallize in the  $\beta$  form. These initial  $\beta$  form crystals 9 are indicated in Figure 10 within a pressurized molten wax 3. Upon leaving chamber 15 the  $\beta$  form crystals 10 would serve as nucleation centers for further ordering of the molecules so that, as the wax cooled and solidified, it would crystallize principally in the  $\beta$  polymorphic form. By this mechanism, more  $\beta$  form crystals 10 are created by each successive application of force by the piston stroke cycles, thereby providing a larger number of  $\beta$  form nucleation centers. At some point the concentration of  $\beta$  form nucleation centers 10 would be sufficient to cause the resolidification of the molten wax completely in the  $\beta$  form. Applicant, however, does not rule out as a possible mechanism the alternative possibility that it is the release of pressure during the piston's negative displacement or release of the pressurized wax through the check valve which initiates  $\beta$  form crystal formation.

On the other hand, the force may work through means other than pressure to transform the waxes. That some other mechanism is at work is suggested by the fact that the force generated by ultrasound also transforms the molten waxes. Ultrasound is usually considered to work its effects through the creation of cavitation bubbles in the medium, although pre-cavitation oscillation of the medium occurs. The collapse of cavitation bubbles is accompanied by localized shock waves, shear forces, and abrupt temperature spikes. Perhaps it is the force applied by shear, shock wave, or heating produced by either the piston cycle or ultrasound that transforms the waxes. Applicant has discovered the effect but does not know the mechanism.

Additional odor tests of choline chloride capsules with transformed tristearin shells indicate that the transformed tristearin shell also forms a better barrier to the transmission of odors than does native tristearin. In taste tests, the taste of the choline chloride was found to be masked by the transformed tristearin until the transformed tristearin shell dissolved. Photomicrographs of choline chloride capsules taken by a scanning electron microscope show that the crystals of choline chloride in the core were completely coated with transformed tristearin when the capsules were made with a 75%/25% weight ratio of core to shell material.

Photomicrographs of capsules formed with a 50%/50% weight ratio of core to transformed wax shell material show significantly enlarged capsules having enlarged shell thickness. The thicker shell improves the handling characteristics of the capsules. Not only is the larger capsule more easily filtered, but it is less likely to provoke respiratory problems when handled.

Choline chloride capsules, formed with transformed tristearin shells, are easily formulated into various tablet sizes, using various tablet filler formulations. The transformed tristearin (all  $\beta$  polymorph) material forms a stable shell about the capsules which in turn yield a far better and more stable tablet for human oral use. Choline chloride capsules formed with native tristearin shells tend to pick up far too much moisture from ambient room humidity during processing into tablets, present more tableting problems, and produce unstable tablets. Choline chloride capsules with transformed tristearin shells tend to pick up moisture at a much slower rate, thereby allowing the capsules to remain "dry" during the tableting process.

While only one example has been provided in this specification, that of choline chloride encapsulated with the transformed triglyceride, tristearin, it should be obvious to anyone skilled in the art that other environmentally sensitive materials may be encapsulated by

the method of this invention using tristearin or other waxes which have been transformed by being subjected to force.

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I claim:

1. A capsule comprising:
  - (a) at least one core material; and
  - (b) a shell comprised of a wax which has been
- 5 subjected to force while in the liquid phase.
2. The capsule of claim 1 wherein said core material comprises an environmentally sensitive substance.
3. The capsule of claim 2 wherein said environmentally sensitive substance comprises a hygroscopic and/or
- 10 deliquescent substance.
4. The capsule of claim 3 wherein said hygroscopic and/or deliquescent substance is choline chloride.
5. The capsule of claim 2 wherein said environmentally sensitive substance comprises a vitamin.
- 15 6. The capsule of claim 1 wherein said wax is subjected to the force of at least one piston stroke cycle.
7. The capsule of claim 6 wherein said wax is glyceryl tristearate.
8. The capsule of claim 7 wherein said glyceryl
- 20 tristearate solidifies substantially in the  $\beta$  polymorphic form.
9. The capsule of claim 1 wherein said wax is subjected to the force of ultrasound.
10. The capsule of claim 9 wherein said wax is glyceryl
- 25 tristearate.
11. The capsule of claim 10 wherein said glyceryl tristearate solidifies substantially in the  $\beta$  polymorphic form.
12. A capsule comprising:
  - (a) at least one core material; and
  - (b) a shell comprised of a wax which has been
- 30 subjected to pressure while in the liquid phase.
13. The capsule of claim 12 wherein said core material comprises an environmentally sensitive substance.
- 35 14. The capsule of claim 13 wherein said environmentally sensitive substance is a hygroscopic and/or deliquescent substance.



15. The capsule of claim 14 wherein said hygroscopic and/or deliquescent substance is choline chloride.

16. The capsule of claim 13 wherein said environmentally sensitive substance is a vitamin.

5 17. The capsule of claim 12 wherein said wax, while in a liquid phase, is subjected to the pressure applied by at least one piston stroke cycle.

18. The capsule of claim 17 wherein said wax is glyceryl tristearate.

10 19. The capsule of claim 18 wherein said glyceryl tristearate solidifies substantially in the  $\beta$  polymorphic form.

20. The capsule of claim 12 wherein said wax is subjected to the pressure applied by ultrasound.

15 21. The capsule of claim 20 wherein said wax is glyceryl tristearate.

22. The capsule of claim 21 wherein said glyceryl tristearate solidifies substantially in the  $\beta$  polymorphic form.

20 23. A capsule comprising:

- (a) at least one core material; and
- (b) a shell comprised of a wax which has been subjected to a shock wave while in the liquid phase.

24. The capsule of claim 23 wherein said core material  
25 comprises an environmentally sensitive substance.

25. The capsule of claim 24 wherein said environmentally sensitive substance is a hygroscopic and/or deliquescent substance.

26. The capsule of claim 25 wherein said hygroscopic  
30 and/or deliquescent substance is choline chloride.

27. The capsule of claim 24 wherein said environmentally sensitive substance is a vitamin.

28. The capsule of claim 23 wherein said wax is subjected to a shock wave applied by at least one piston  
35 stroke cycle.

29. The capsule of claim 28 wherein said wax is glyceryl tristearate.

30. The capsule of claim 29 wherein said glyceryl tristearate solidifies substantially in the  $\beta$  polymorphic form.

31. The capsule of claim 23 wherein said wax, while in the molten phase, is subjected to a shock wave applied by ultrasound.

32. The capsule of claim 31 wherein said wax is glyceryl tristearate.

33. The capsule of claim 32 wherein said glyceryl tristearate solidifies substantially in the  $\beta$  polymorphic form.

34. A capsule comprising:

(a) at least one core material; and

(b) a shell comprised of a wax which has been subjected to shear while in the liquid phase.

35. The capsule of claim 34 wherein said core material comprises an environmentally sensitive substance.

36. The capsule of claim 35 wherein said environmentally sensitive substance is a hygroscopic and/or deliquescent substance.

37. The capsule of claim 36 wherein said hygroscopic and/or deliquescent substance is choline chloride.

38. The capsule of claim 35 wherein said environmentally sensitive substance is a vitamin.

39. The capsule of claim 34 wherein said wax is subjected to shear applied by at least one piston stroke cycle.

40. The capsule of claim 39 wherein said wax is glyceryl tristearate.

41. The capsule of claim 40 wherein said glyceryl tristearate solidifies substantially in the  $\beta$  polymorphic form.

42. The capsule of claim 34 wherein said wax, while in the liquid phase, is subjected to shear applied by ultrasound.

43. The capsule of claim 42 wherein said wax is glyceryl tristearate.

44. The capsule of claim 43 wherein said glyceryl tristearate solidifies substantially in the  $\beta$  polymorphic form.

45. A capsule comprising:

- 5 (a) a choline chloride core; and  
(b) a shell comprising glyceryl tristearate which has been subjected to force, while in the liquid phase, applied by at least one piston stroke cycle.

46. The capsule of claim 45 wherein the glyceryl  
10 tristearate has solidified substantially in the  $\beta$  polymorphic form.

47. A capsule comprising:

- 15 (a) a choline chloride core; and  
(b) a shell comprising glyceryl tristearate which has been subjected to force, while in the liquid phase, applied by ultrasound.

48. The capsule of claim 47 wherein the glyceryl tristearate has solidified substantially in the  $\beta$  polymorphic form.

20 49. A method for encapsulating core materials comprising the following steps:

- (a) placing in a mixing container the core material and a liquid shell material comprised of wax which has been transformed, while in the liquid phase, by being  
25 subjected to force;

(b) mechanically mixing the core material and wax shell material; and

(c) solidifying the wax wherein the mechanical mixing causes the wax shell  
30 material to coat and encapsulate the core material.

50. The method of claim 49 wherein said core material is an environmentally sensitive substance.

51. The method of claim 50 wherein said environmentally sensitive core material is a hygroscopic or deliquescent  
35 substance.

52. The method of claim 51 wherein said hygroscopic or deliquescent substance is choline chloride.

53. The method of encapsulating core materials of claim 49 wherein said wax is transformed by being subjected to the force of at least one piston stroke cycle.

54. The method of claim 53 wherein said transformed wax  
5 is glyceryl tristearate.

55. The method of encapsulating materials of claim 49 wherein said wax is transformed by being subjected to the force of ultrasound.

56. The method of claim 55 wherein said transformed wax  
10 is glyceryl tristearate.

57. The method of claim 49 comprising the further step of preheating said core material prior to mixing said core material with said transformed liquid wax shell material to a temperature less than the temperature of said liquid wax  
15 with which the core material will be combined.

58. The method of claim 49 wherein said solidifying step is performed at the same time as the mechanical mixing of said core and shell material.

59. A capsule having a core material surrounded by a  
20 wax shell made by the following method:

(a) transforming the wax while in a liquid phase by subjecting the wax to a force;

(b) placing in a mixing container the core material and the transformed liquid wax;

25 (c) mechanically mixing said core material and said transformed liquid wax; and

(d) solidifying the wax wherein the liquid wax coats the core material and hardens and encapsulates the core material.

30 60. The capsule of claim 59 wherein the wax to be transformed is melted before being transformed.

61. The capsule of claim 60 wherein the wax is glyceryl tristearate.

35 62. The capsule of claim 59 wherein the core material is an environmentally sensitive substance.

63. The capsule of claim 62 wherein the environmentally sensitive substance is a hygroscopic or deliquescent

substance.

64. The capsule of claim 63 wherein said hygroscopic or deliquescent substance is choline chloride.

65. The capsule of claim 59 wherein the step of  
5 transforming the wax by subjecting the wax to force further comprises the following steps:

(a) placing the wax in a chamber attached to a piston;

(b) cycling the piston against the wax at least  
10 one cycle; and

(c) removing the transformed wax from the chamber wherein the at least one piston stroke cycle transforms the wax.

66. The capsule of claim 65 wherein the wax to be  
15 transformed is melted before being transformed.

67. The capsule of claim 59 wherein the step of subjecting the wax to force further comprises the following steps:

(a) placing the wax in a holding vessel;  
20 (b) immersing an ultrasonic transducer in the wax;  
(c) applying ultrasound to the wax; and  
(d) removing the transformed wax from the holding vessel

wherein the ultrasound transforms the wax.

68. The capsule of claim 67 wherein the wax to be  
25 transformed is melted before being transformed.

69. A capsule comprising:

(a) a core; and  
(b) a shell formed from a triglyceride solidified  
30 substantially in the  $\beta$  polymorphic form wherein the shell surrounds and encloses the core material.

70. The capsule of claim 69 in which said shell is composed of glyceryl tristerate.

71. The capsule of claim 69 in which said core  
35 comprises an environmentally sensitive substance.

72. The capsule of claim 71 in which said

environmentally sensitive substance comprises a hygroscopic and/or deliquescent substance.

73. The capsule of claim 72 in which said hygroscopic and/or deliquescent substance is choline chloride.

5 74. A capsule comprising:

- (a) a core of choline chloride; and
- (b) a shell formed from glyceryl tristearate solidified substantially in the  $\beta$  polymorphic form wherein the shell surrounds and encloses the core.

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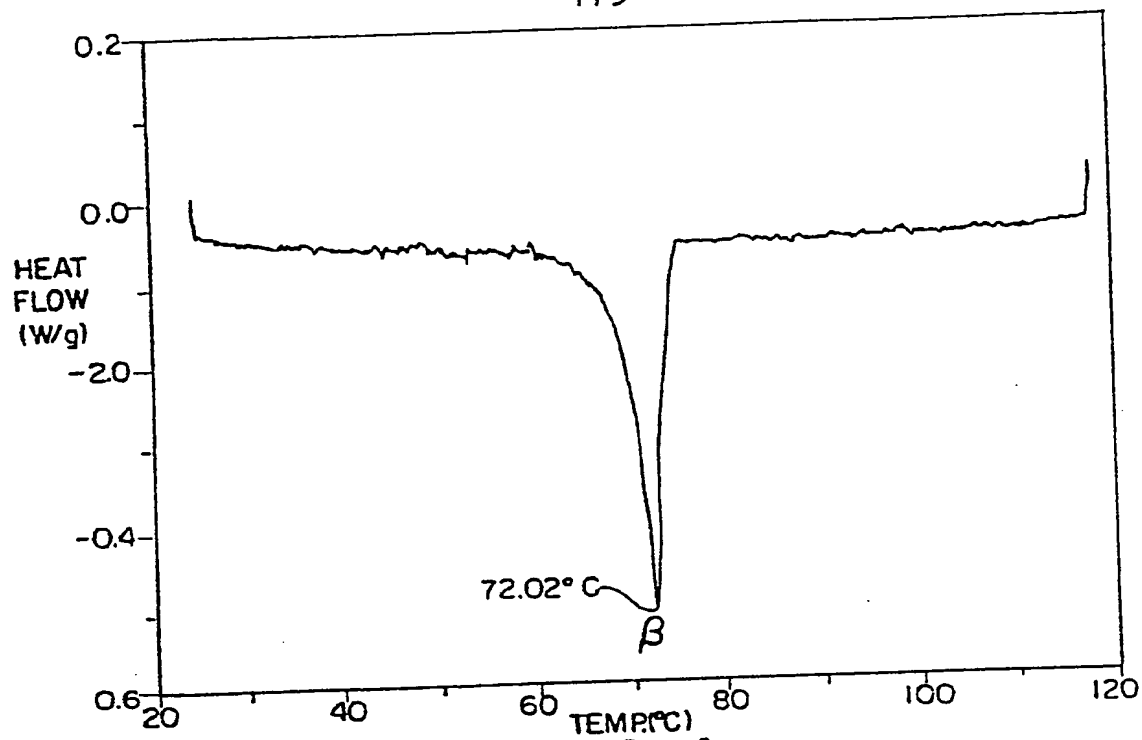


FIG. 1

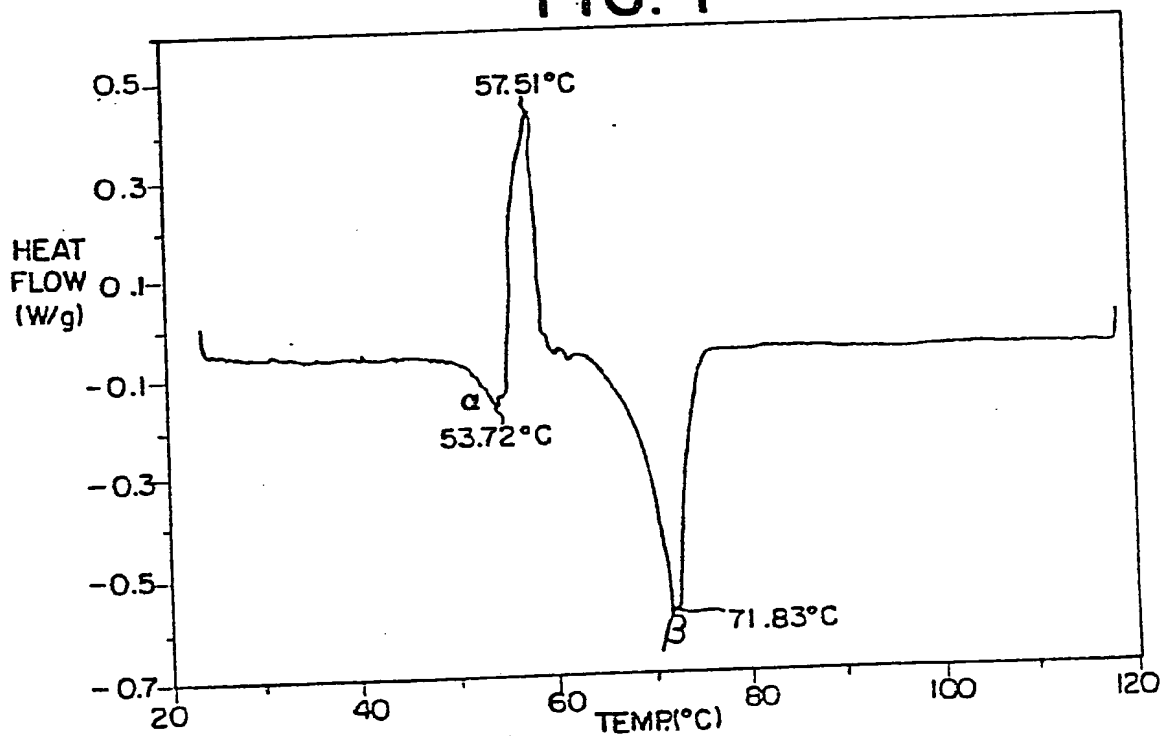


FIG. 2

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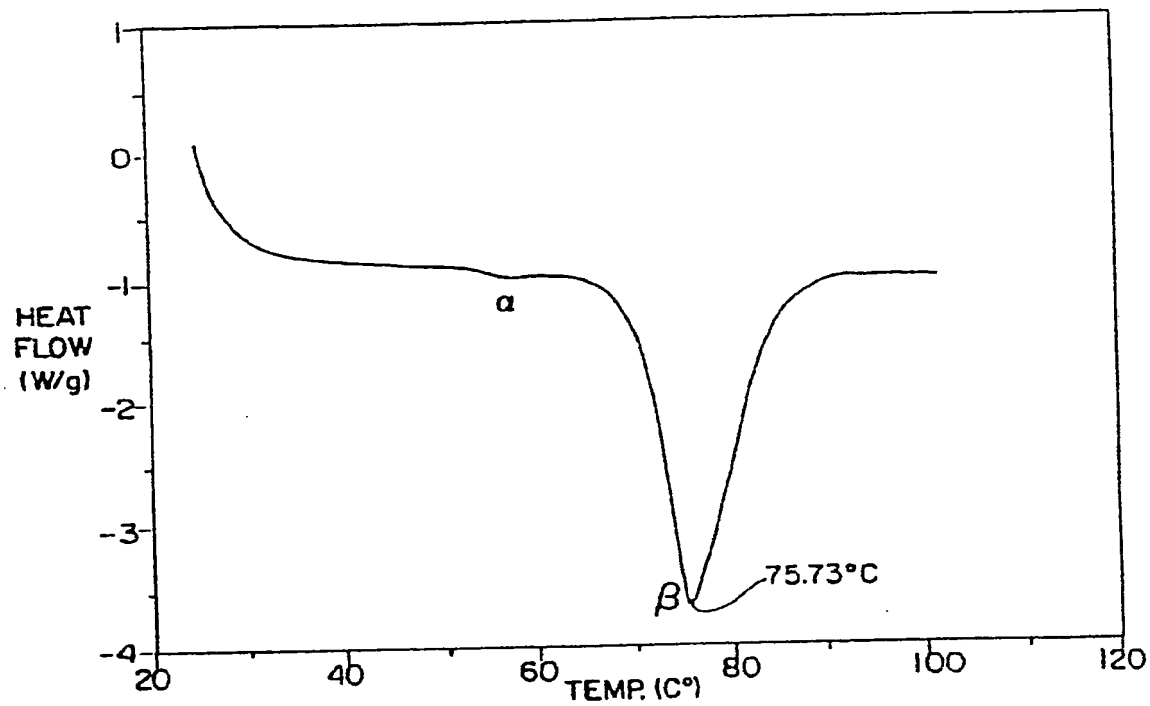


FIG. 3

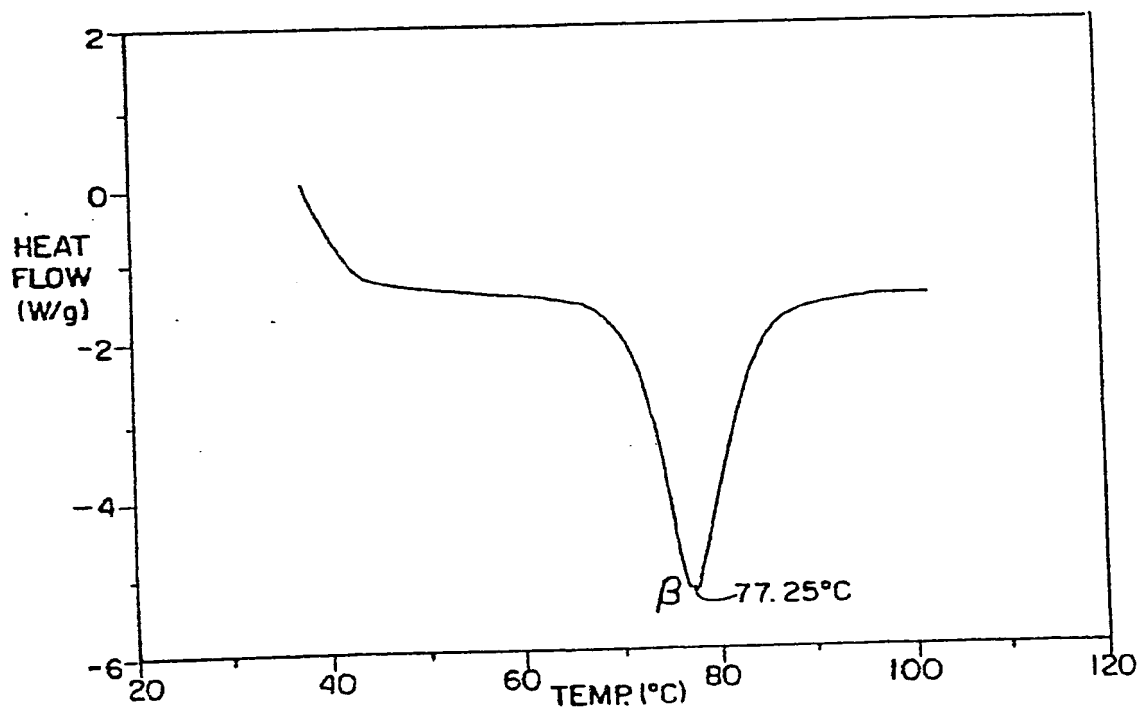


FIG. 4

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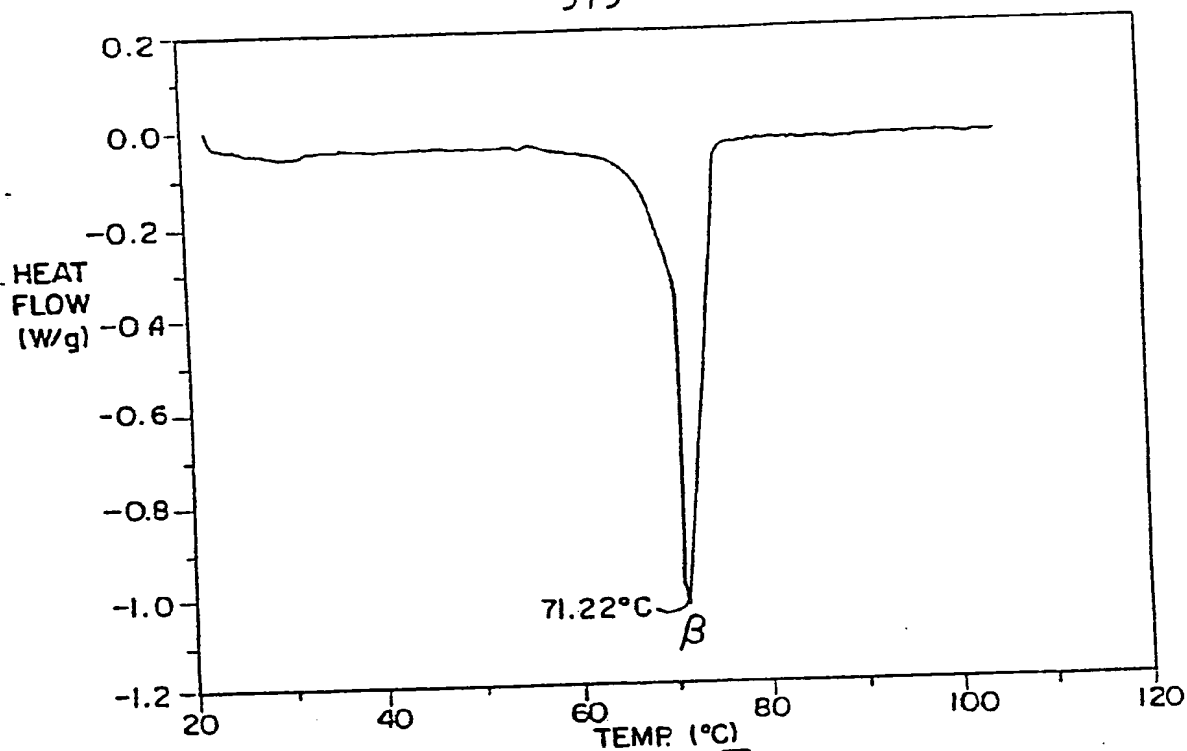


FIG. 5

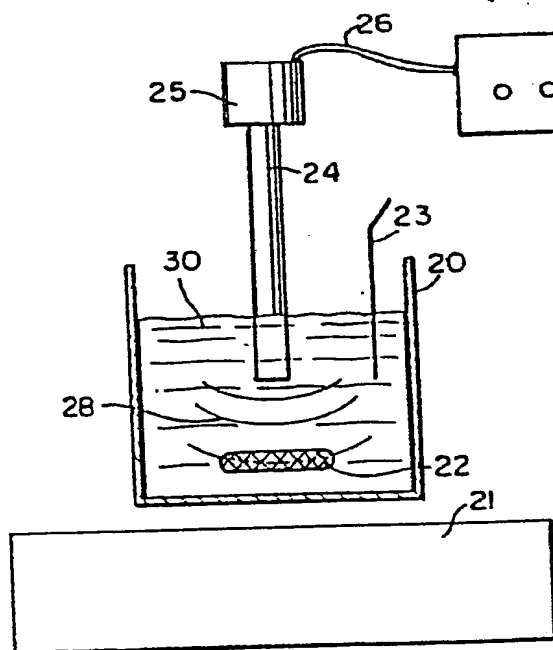


FIG. 8

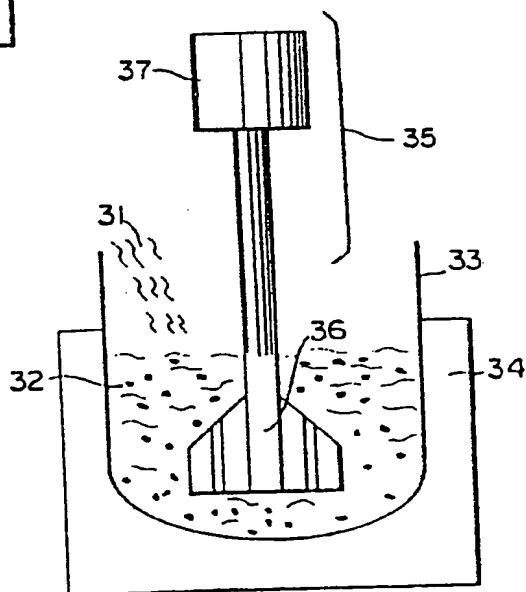


FIG. 9

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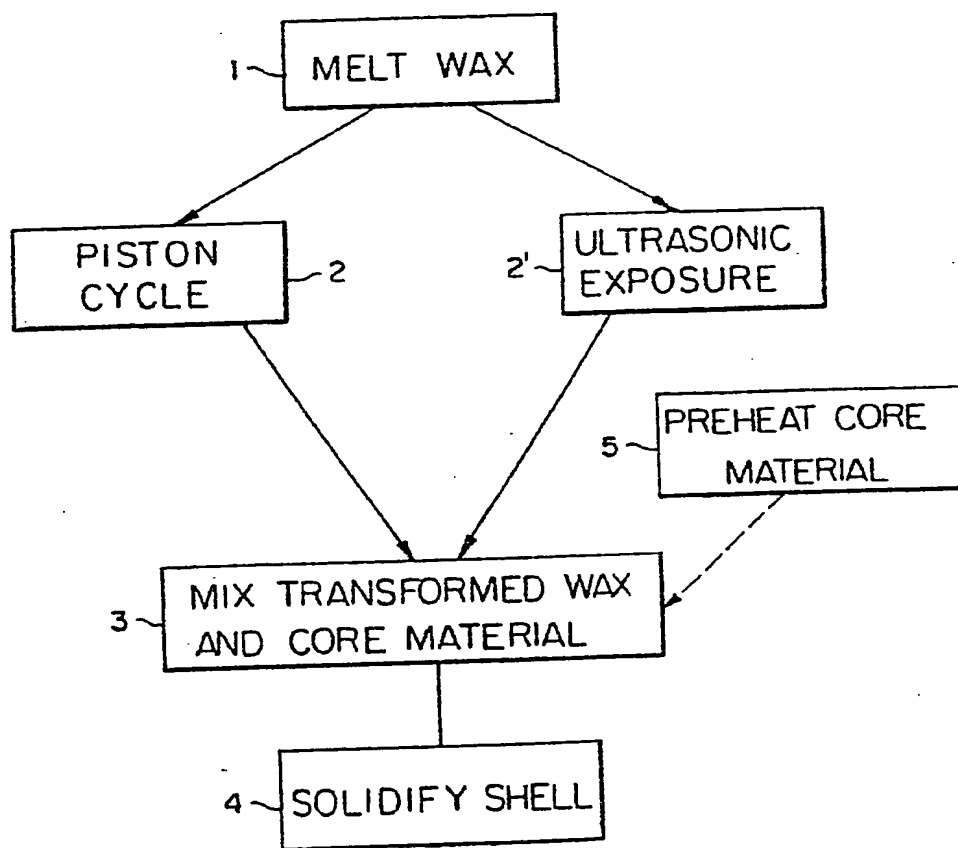
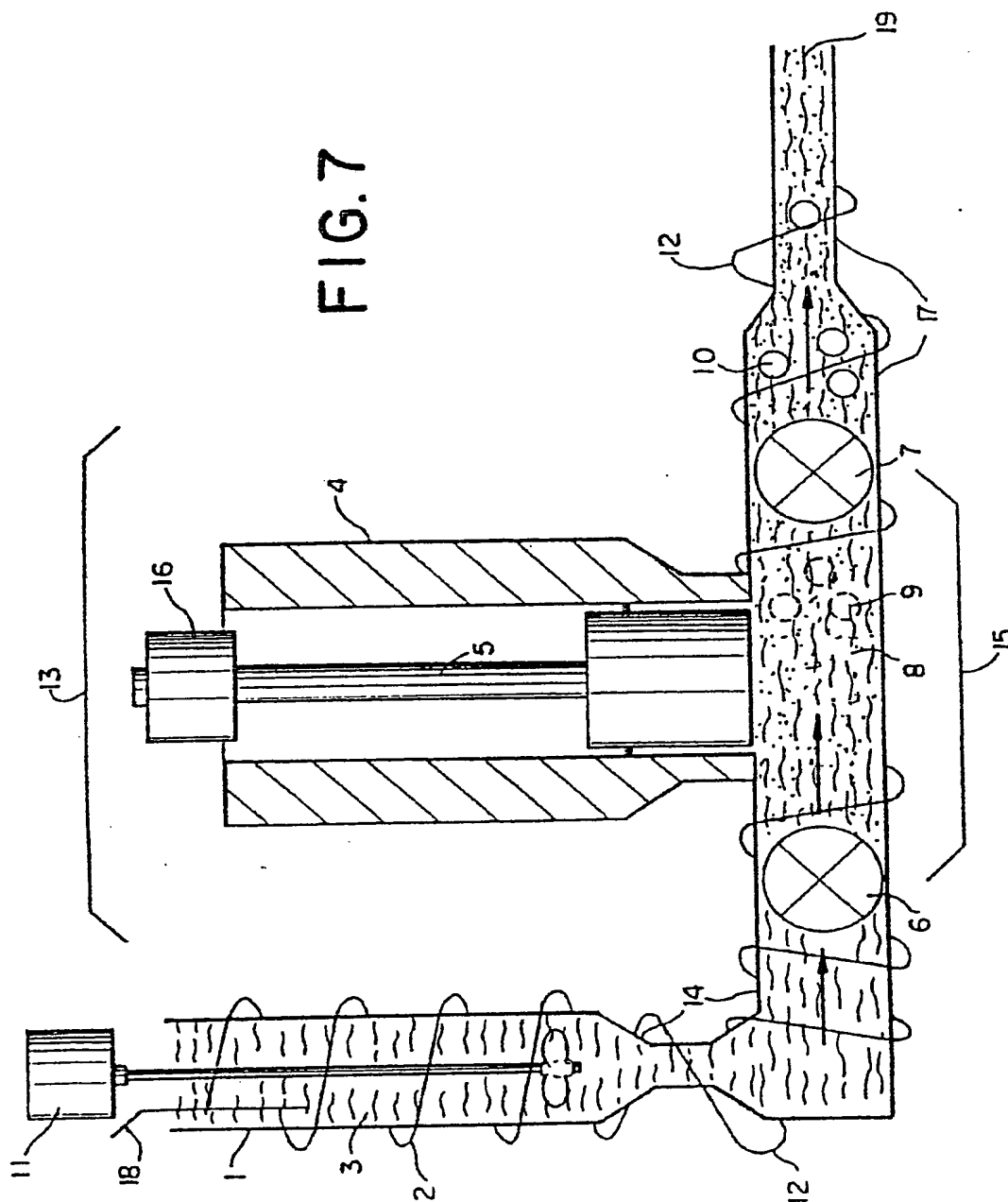


FIG. 6

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5/5

FIG. 7



SUBSTITUTE SHEET

# INTERNATIONAL SEARCH REPORT

International Application No. P0 891/02372

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all):

According to International Patent Classification (IPC) or to both National Classification and IPC  
 IPC(5): A61K 9/48  
 U.S. CL: 424/451

## II. FIELDS SEARCHED

Minimum Documentation Searched:

Classification System:

Classification Symbols

U.S. 424/451

Documentation Searched other than Minimum Documentation  
 to the extent that such documents are included in the fields searched:

## III. DOCUMENTS CONSIDERED TO BE RELEVANT:

Category \* | Citation of Document, with indication, where appropriate, of the relevant passages: | Relevant to Claim No. \*\*

Y	US, A, 2,690,038 (STIRN) 28 SEPTEMBER 1954 See entire document.	1-8,12-19,28- 30,39-41,45- 46,49-52,57- 64, and 69-74
Y	CA, A, 1,225,861 (ANDO) 25 AUGUST 1987 See entire document.	1-8,12-19,23- 30,39-41,45- 46,49-52,57- 64 and 69-74
Y	US, A, 4,788,180 (BLOCH) 29 NOVEMBER 1988 See entire document.	1-8,12-19,28- 30,39-41,45, 46,49-52,57- 64 and 69-74
Y	US, A, 3,791,856 (DULING) 12 FEBRUARY 1974 See entire document.	1,9-11,20-22, 31-33,42-44, 47-48,55-56, 67-68

\* Special categories of cited documents: 13

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search:

09 July 1991

International Searching Authority:

ISA/US

Date of Mailing of this International Search Report:

21 AUG 1991

Signature of Authorized Officer:

William E. Benston, Jr.

## FURTHER INFORMATION CONTAINED FROM THE SECOND SHEET

Y

US, A, 3,844,829 (BLACK) 9 OCTOBER 1974  
See entire document

1,6,17-19,  
23-30, 39,  
45-46,53-54,  
65-66

V ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers \_\_\_\_\_ because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim numbers \_\_\_\_\_ because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim numbers \_\_\_\_\_ because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple inventions in this international application:

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all the claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report covers the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority invites payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

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